

# New Agents for Chronic HCV

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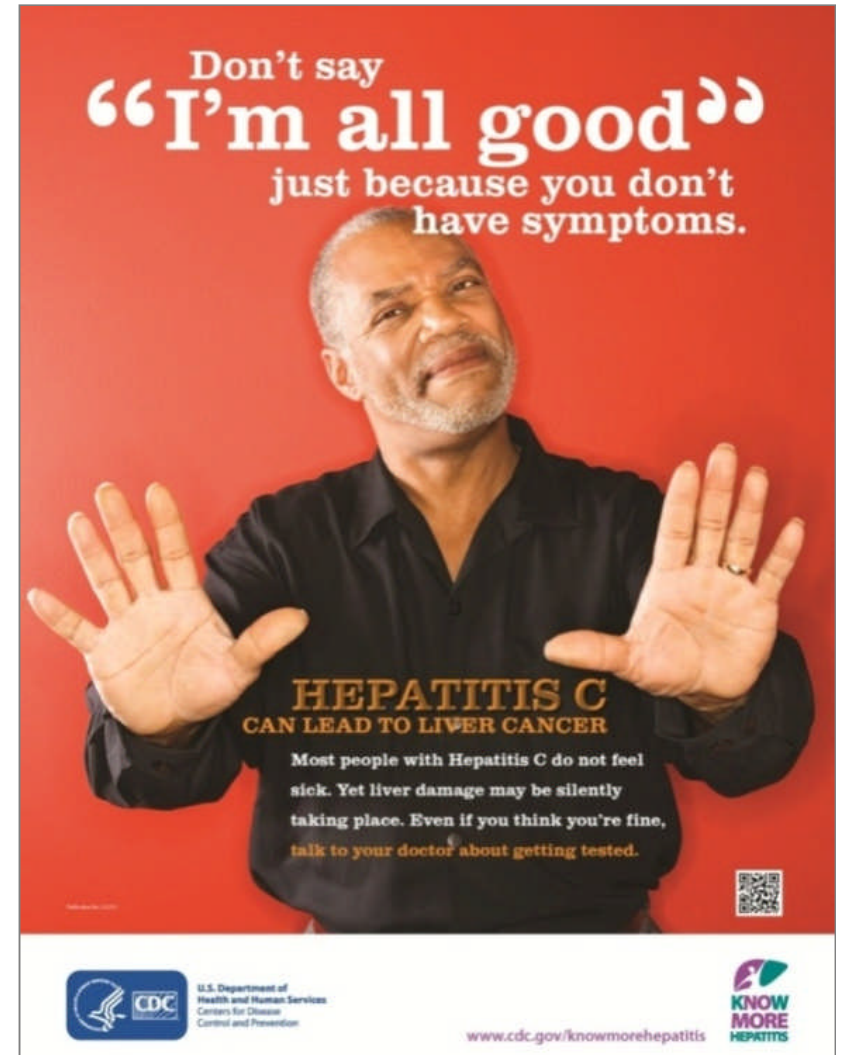


# Disclosures

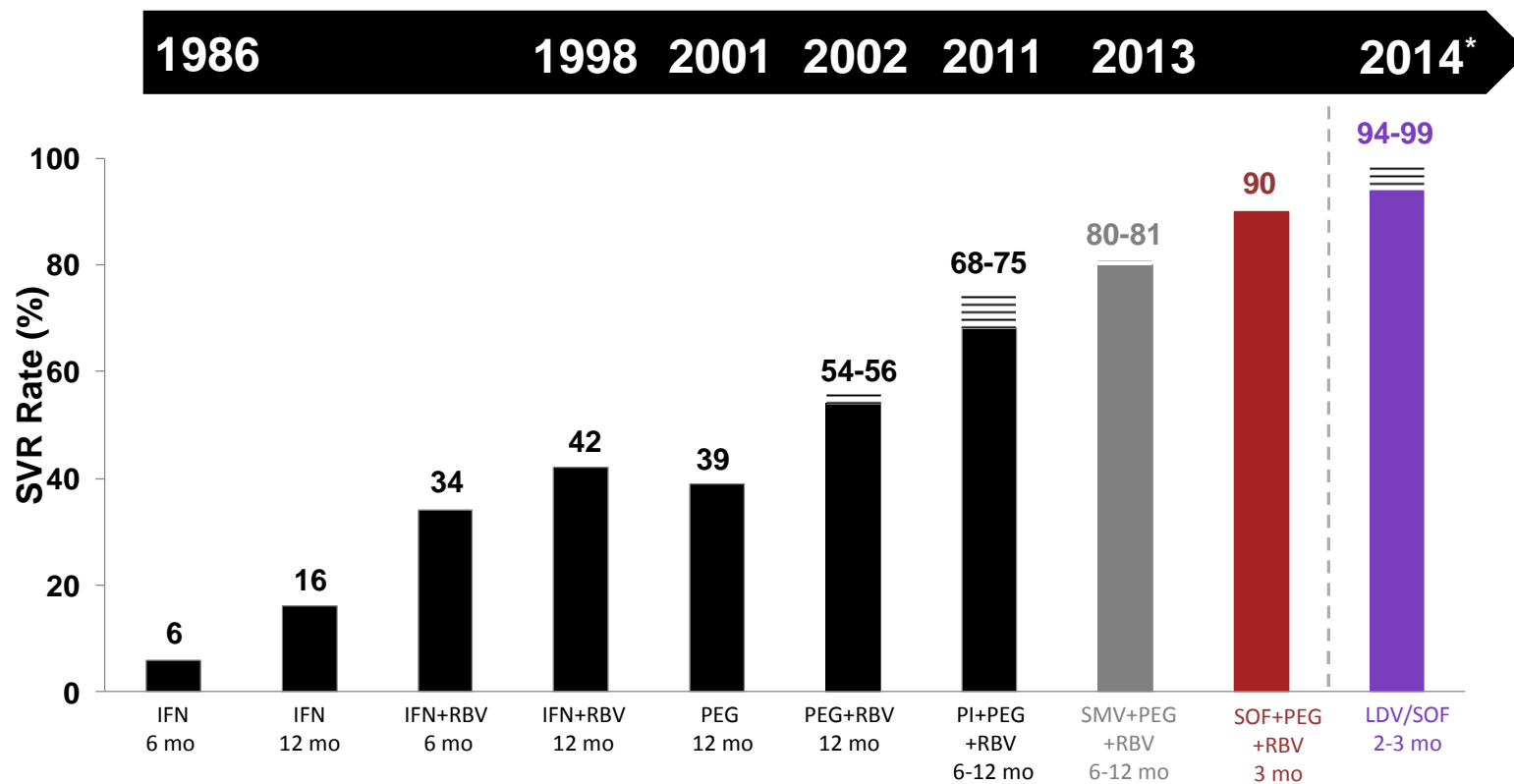
- This seminar contains off-label and investigational medications.
- HCV Research Support/Grants or Speakers' Bureaus/Advisory Boards: Merck, Gilead, Janssen, Genentech, Kadmon, Vertex, AbbVie, Bristol-Meyers Squibb.
- Other financial relationships not relevant to this talk: DiaPharma, Connatus, Intercept, Lumena, Zeon Chemicals, NIH 1R01ES021375, K23AA18399, 1R13ES024661, CDC/ATSDR: #200-2013-M-57311.

# Objectives

## 1) New Agents for Hepatitis C.



## SVR Rates in HCV Genotype 1 Treatment-Naïve Patients

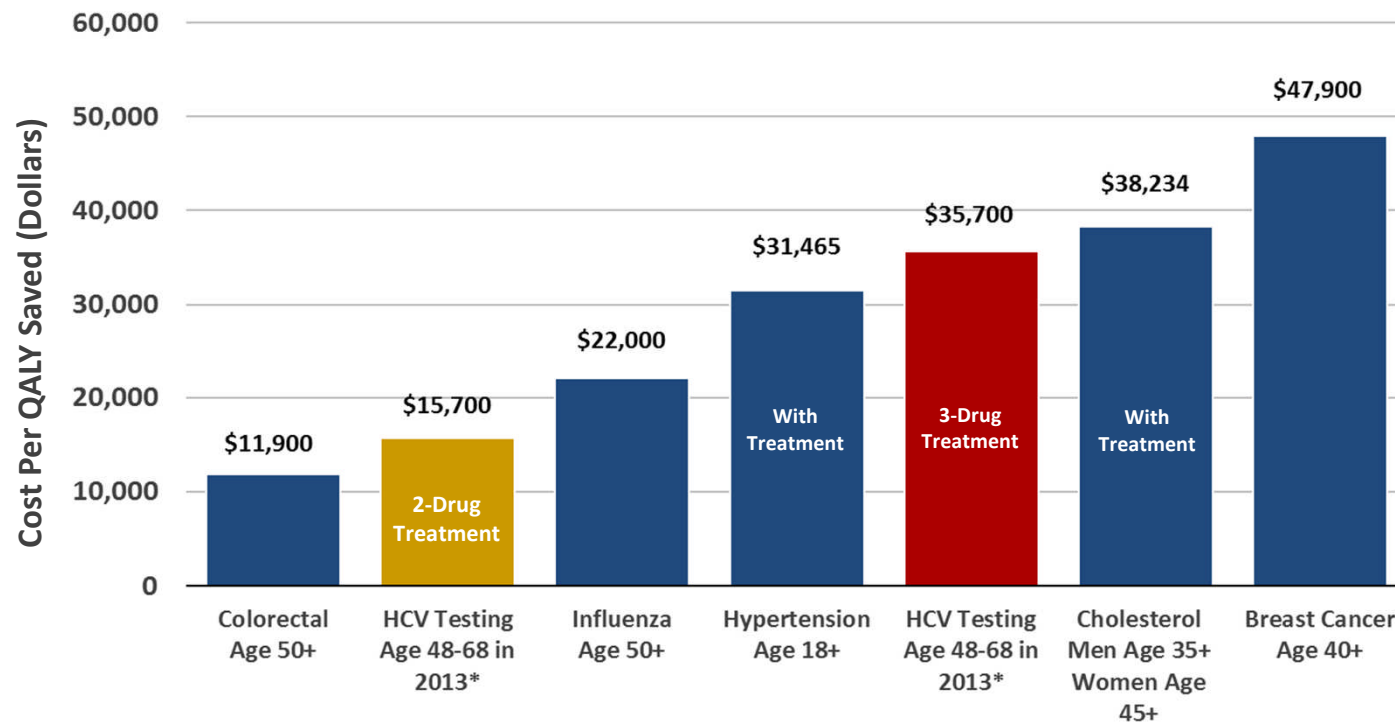


\*Year of data presentation at EASL 2014 and publication in *NEJM*

Adapted from Strader DB, et al. *Hepatology* 2004;39:1147-71. INCIVEK [PI]. Cambridge, MA: Vertex Pharmaceuticals; 2013. VICTRELIS [PI]. Whitehouse Station, NJ: Merck & Co; 2014. Jacobson I, et al. EASL 2013. Amsterdam. The Netherlands. Poster #1425. Manns M, et al. EASL 2013. Amsterdam. The Netherlands. Oral #1413. Lawitz E, et al. APASL 2013. Singapore. Oral #LB-02; Afdhal N, et al. *N Engl J Med* 2014; 2014 Apr 12 [Epub ahead of print]; Kowdley K, et al. *N Engl J Med* 2014; 2014 Apr 11 [Epub ahead of print]



# Cost-Effectiveness of HCV Testing vs Other Routine Preventive Services



\*Birth cohort testing, 1945-1965.

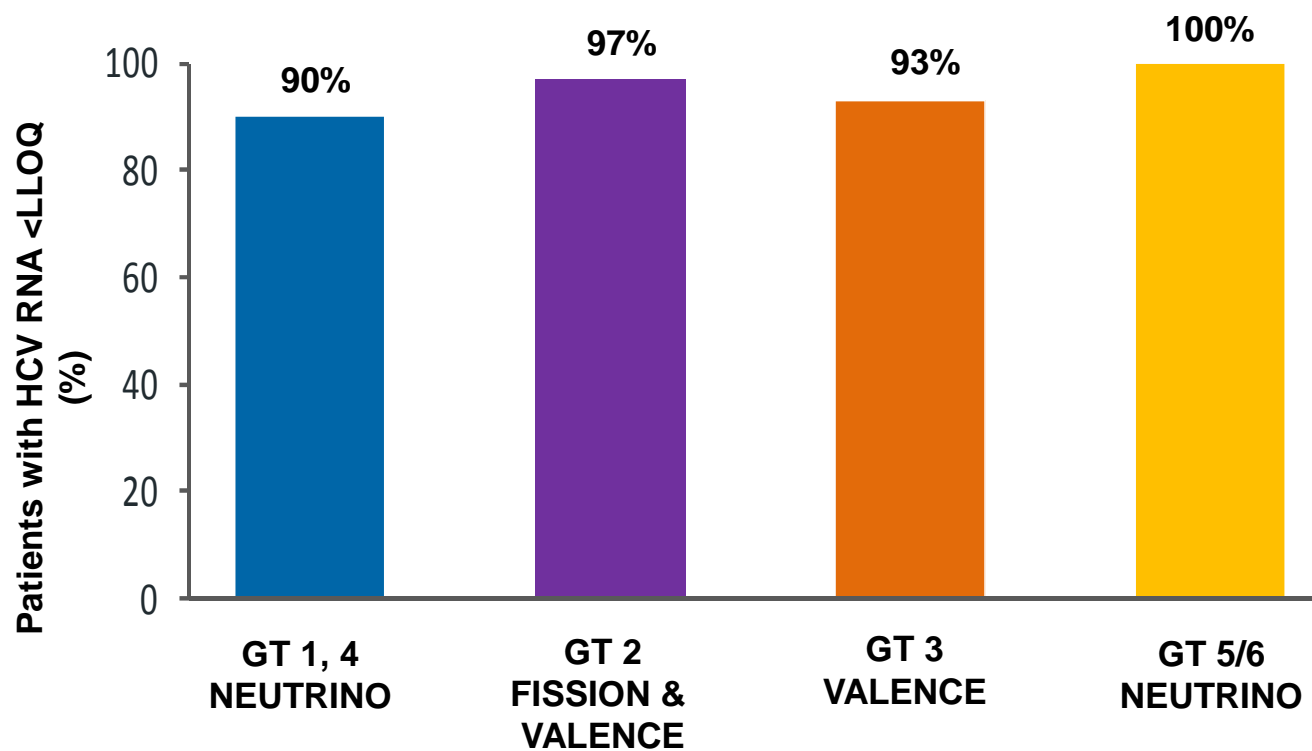
2-drug treatment=PegIFN+RBV; 3-drug treatment=PegIFN+RBV+PI.

QALY=quality-adjusted life-year.

[www.prevent.org/National-Commission-on-Prevention-Priorities/Rankings-of-Preventive-Services-for-the-US-Population.aspx](http://www.prevent.org/National-Commission-on-Prevention-Priorities/Rankings-of-Preventive-Services-for-the-US-Population.aspx).

Rein DB, et al. *Ann Intern Med.* 2012;156:263-270.

Sofosbuvir > 90% SVR 12 Across Treatment-Naïve Genotypes 1, 2, 3, 4, 5, 6.  
Interferon/ribavirin required for genotype 1.



Lawitz E, et al. *N Engl J Med*. 2013 May 16

Lawitz E, et al. APASL 2013. Singapore. Oral #LB-02

Zeuzem S, et al. AASLD 2013. Washington, DC. #1085

# Comorbid Conditions Associated with Decision-Making Regarding HCV Treatment in a Large US HMO

Retrospective study using Kaiser Permanente database to compare characteristics of those treated vs. those not treated for HCV using IFN-based therapy and to identify significant predictors of not receiving treatment

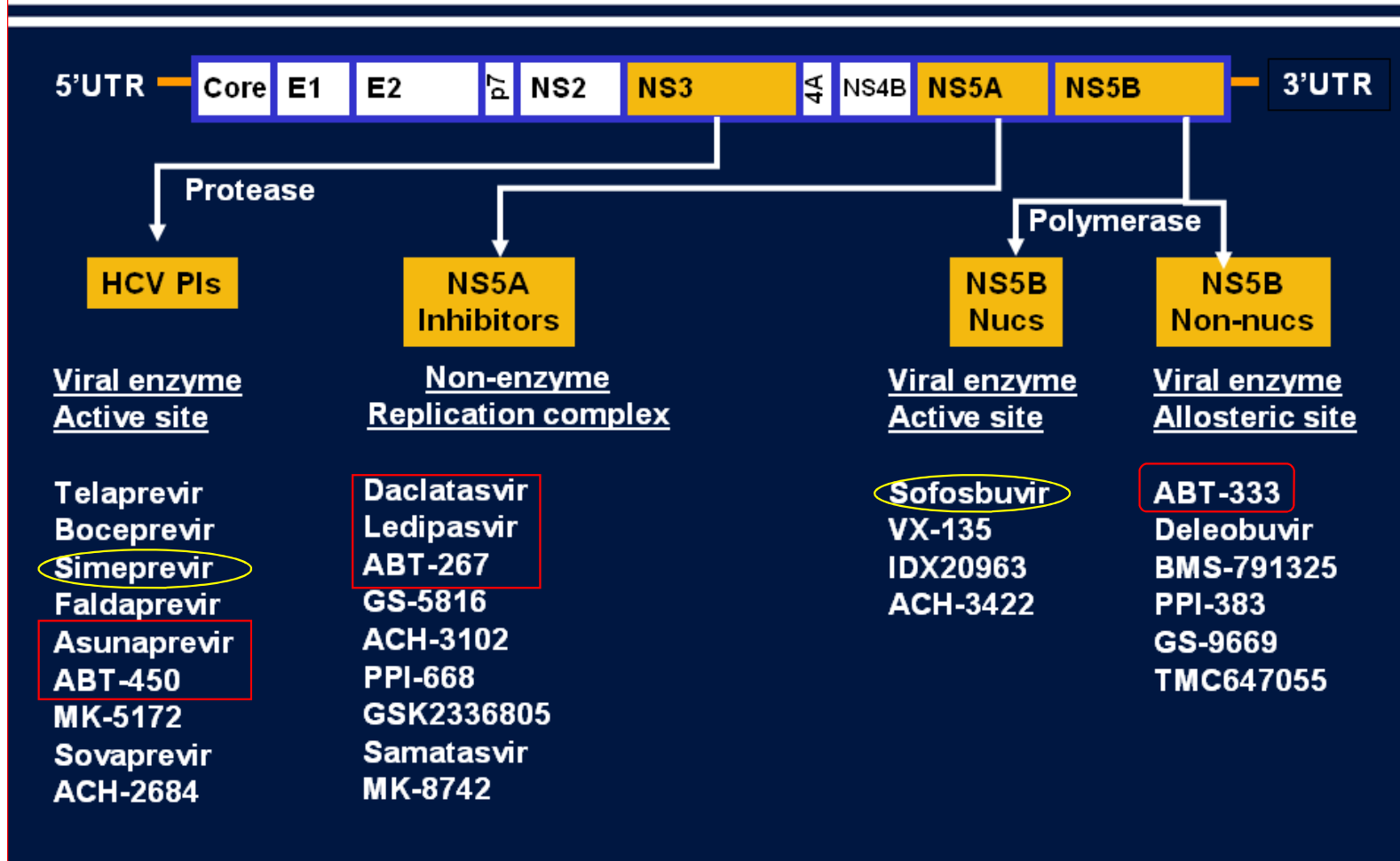
- 15% (7,945/51,984) of the total number of patients identified with HCV were treated
- 42% of the total study population were likely IFN-ineligible or intolerant
- 50% of the study population had a significant comorbid illness
- Factors associated with receiving treatment included age 45–65, male gender, cirrhosis, HIV, NAFLD, depression, prior liver transplant.

Factors Associated with NOT Receiving Treatment

Independent variables	Odds Ratio	P-value
Anemia	0.329	<0.0001
Autoimmune disorder	0.775	0.0035
Renal dysfunction	0.659	0.0195
Cardiovascular disease	0.602	<0.0001
Psychosis/Bipolar	0.678	0.0051
Severe lung disease	0.555	<0.0001
Substance abuse	0.542	<0.0001
MELD ( $\geq 12$ )	0.385	<0.0001

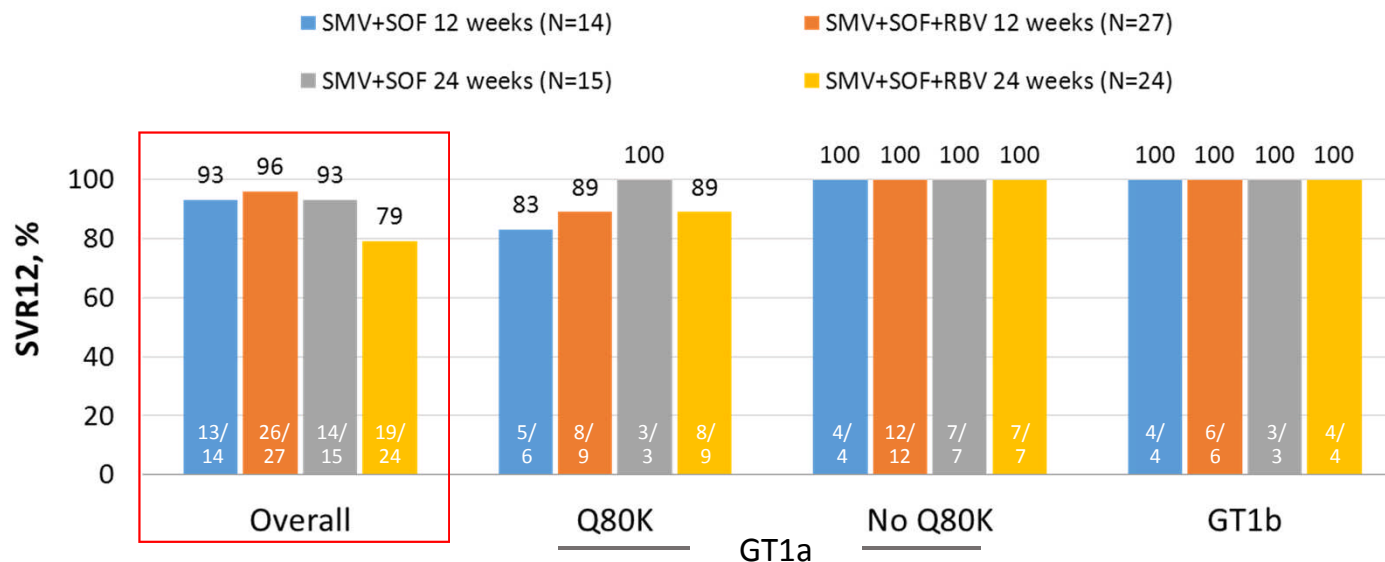


# Multiple Direct Acting Antivirals



COSMOS (SMV+SOF±RBV)

## Simeprevir+Sofosbuvir±Ribavirin for 12-24 Weeks<sup>†</sup> in Prior Null Responders With F0-F2 Fibrosis (Cohort 1)



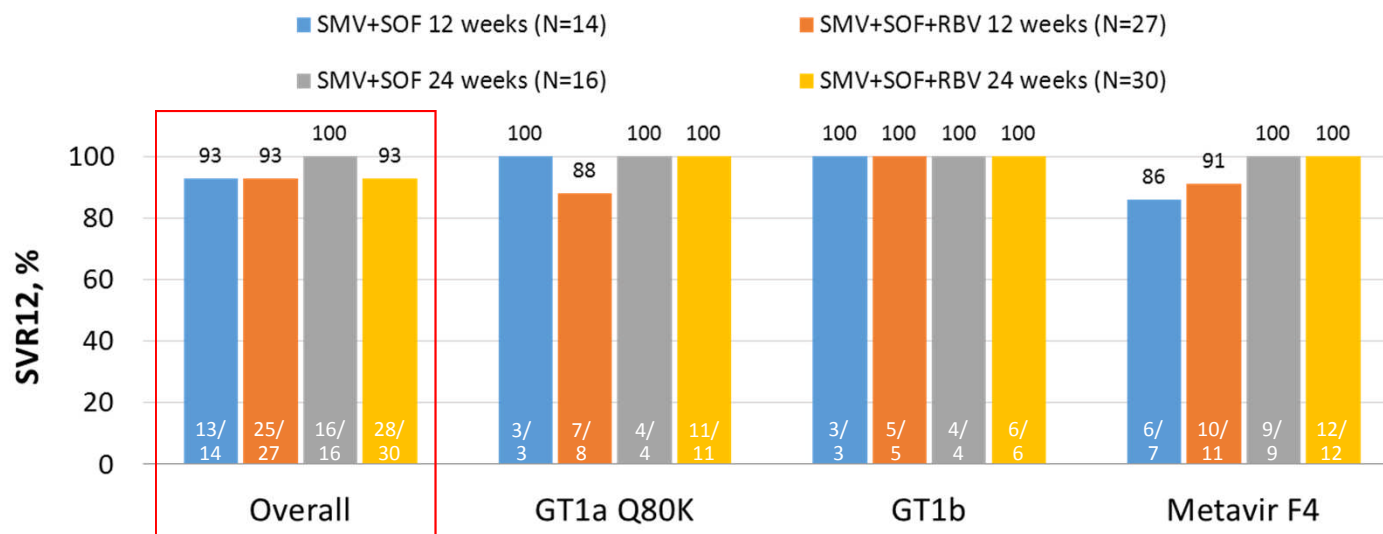
- No viral breakthrough
- 5 non-virologic failures
  - 4 early treatment D/C
  - 1 patient achieved SVR4 but died before SVR12
- Relapse occurred in 3 patients (all GT 1a patients with Q80K polymorphism)

**SMV+SOF RBV for 12 or 24 weeks led to overall SVR rate of 90% in Metavir F0–2 null responders with HCV GT 1**



COSMOS (SMV+SOF±RBV)

# SMV+SOF±RBV in HCV GT 1 Treatment Naïve and Prior Null Responders with F3–4 (Cohort 2)



- No viral breakthrough
- Relapse occurred in 3 GT1a-infected patients (1 with Q80K, 2 without Q80K; all had NS3 mutations)
- Most common AEs: fatigue 37.9%, headache 19.5%
- Four serious AEs reported
- One patient D/C treatment due to AE

**SMV+SOF±RBV led to overall SVR rate of 94% in Metavir F3–F4 naïve and null responders with HCV GT 1**



# UofL – COSMOS Regimen Post Liver Trans



- 24 difficult to treat subjects (19 treatment experienced, 8 advanced fibrosis, 7 Q80K<sup>+</sup>, 19 high viral loads).
- 89% achieved week 4 on treatment viral response (17/19).
- 100% achieved week 8 on treatment viral response (12/12).
- 100% achieved week 12 end of treatment viral response (3/3).
- AEs: 1 death unrelated to treatment, 56% anemia with ribavirin, 50% required CNI dose modification.
- No rejection episodes.

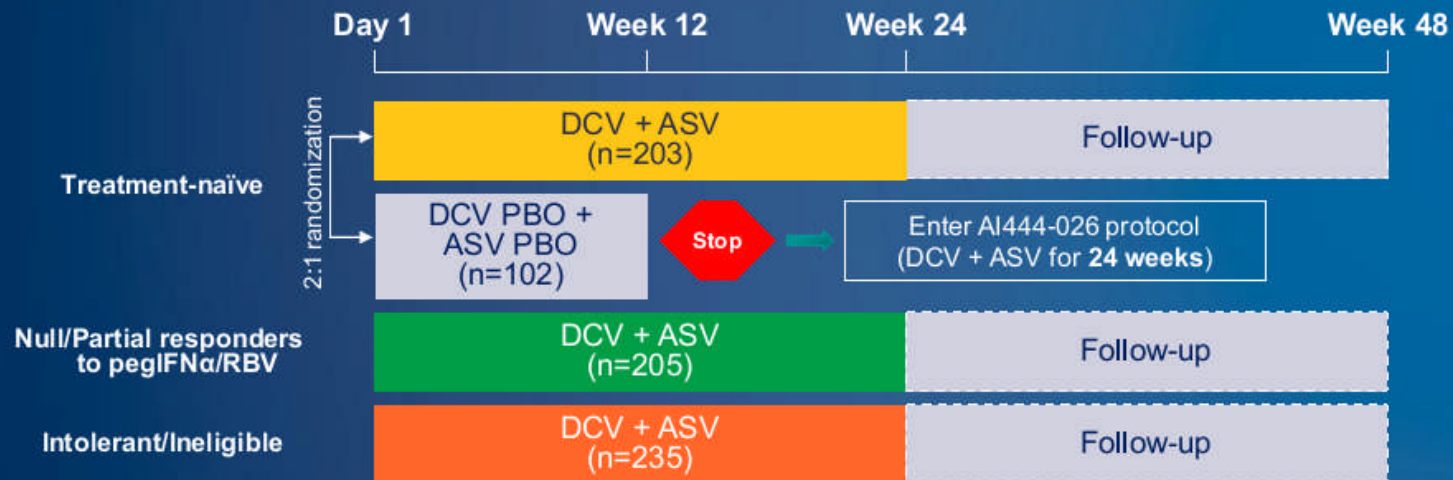


\* Under review at AASLD

## Daclatasvir + Asunaprevir Phase 3 AI447-028 (HALLMARK-DUAL): Study Design

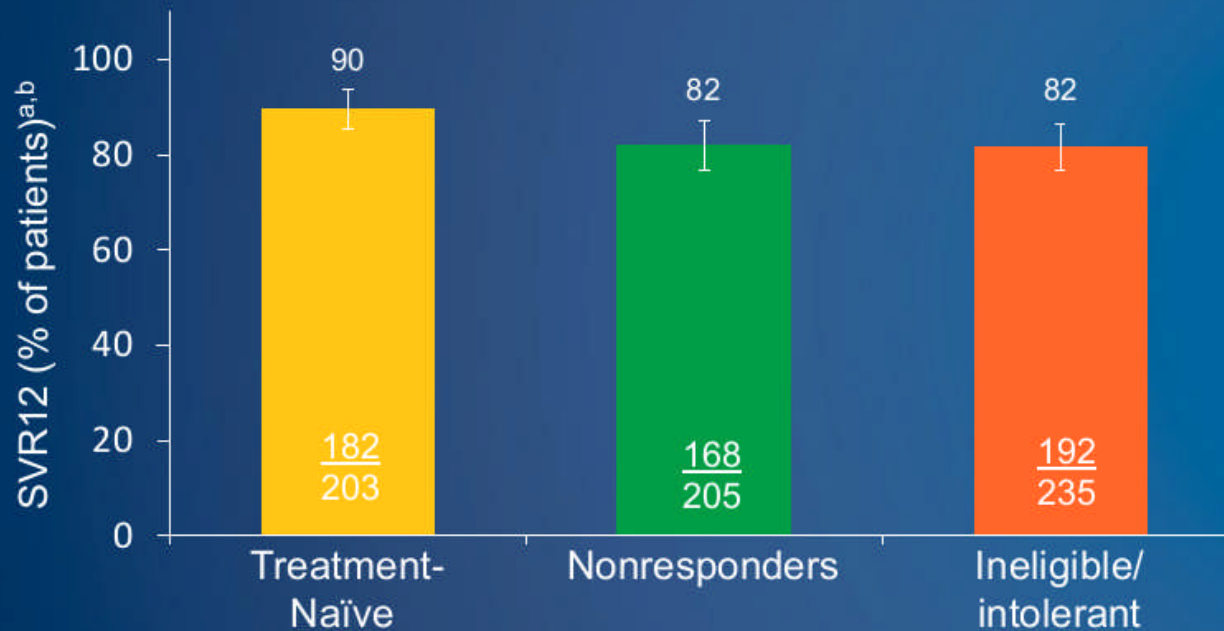
**Study 028:** Open-label, phase 3, randomized trial in GT-1b treatment-naïve, prior nonresponders and pegIFN/RBV-ineligible patients with and without cirrhosis

**Primary endpoint:** SVR12



ASV=asunaprevir; DCV=daclatasvir; PBO=placebo; pegIFNα/RBV=pegylated interferon alfa; RBV=ribavirin;  
SVR=sustained virologic response.  
Manns M et al. 49th EASL 2014. April 9-13. London, UK. Abstract O166.

## Daclatasvir + Asunaprevir Phase 3 AI447-028 (HALLMARK-DUAL): SVR12



84% overall SVR for DCV/ASV 24 weeks 1b.

<sup>a</sup>HCV RNA < lower limit of assay quantitation (25 IU/mL).

<sup>b</sup>Patients with missing SVR12 data counted as treatment failures.

SVR=sustained virologic response.

Manns M et al. 49th EASL 2014. April 9-13. London, UK. Abstract O166.

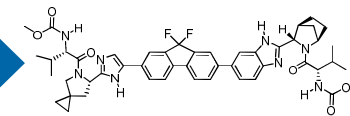
# Ledipasvir/Sofosbuvir: A Single Tablet Regimen (STR) ‡



- **Ledipasvir**

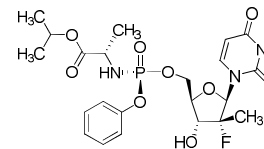
- Picomolar potency against HCV GT 1a and 1b<sup>1</sup>
- Effective against NS5B RAV S282T<sup>2</sup>
- Once-daily, oral, 90 mg

**LDV  
NS5A  
inhibitor**



- **Sofosbuvir**

- Potent antiviral activity against HCV GT 1–6
- High barrier to resistance
- Once-daily, oral, 400-mg tablet



**SOF - NS5B  
nucleotide  
polymerase  
inhibitor**

- **Ledipasvir/Sofosbuvir STR**

- Once-daily, oral fixed-dose (90/400 mg) combination tablet
- No food effect
- >2000 patients treated

**LDV  
NS5A  
inhibitor**

**SOF - NS5B  
nucleotide  
polymerase  
inhibitor**

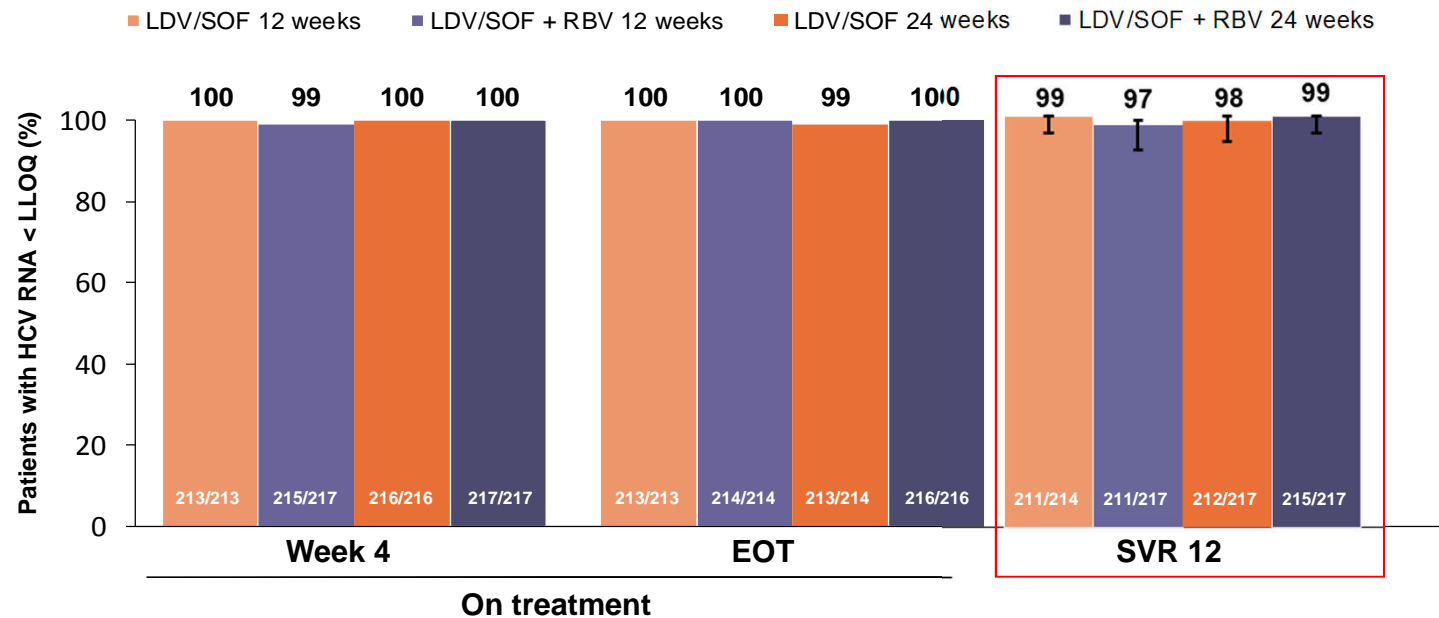
**Priority Review and Breakthrough Status Granted  
PDUFA: Oct 10, 2014**

1. Lawitz E, et al. EASL 2011, poster 1219; 2. Cheng G, et al. EASL 2012, poster 1172

ION-1 (LDV/SOF±RBV)



## LDV/SOF±RBV x 12-24 wks in Treatment-Naïve (including cirrhosis) GT 1 HCV



- All four treatment arms met the primary endpoint of superiority over the historical response rate of 60% ( $P < 0.001$  for all comparisons)
- 16% had NS5A RAVs at baseline, with 96% achieving SVR

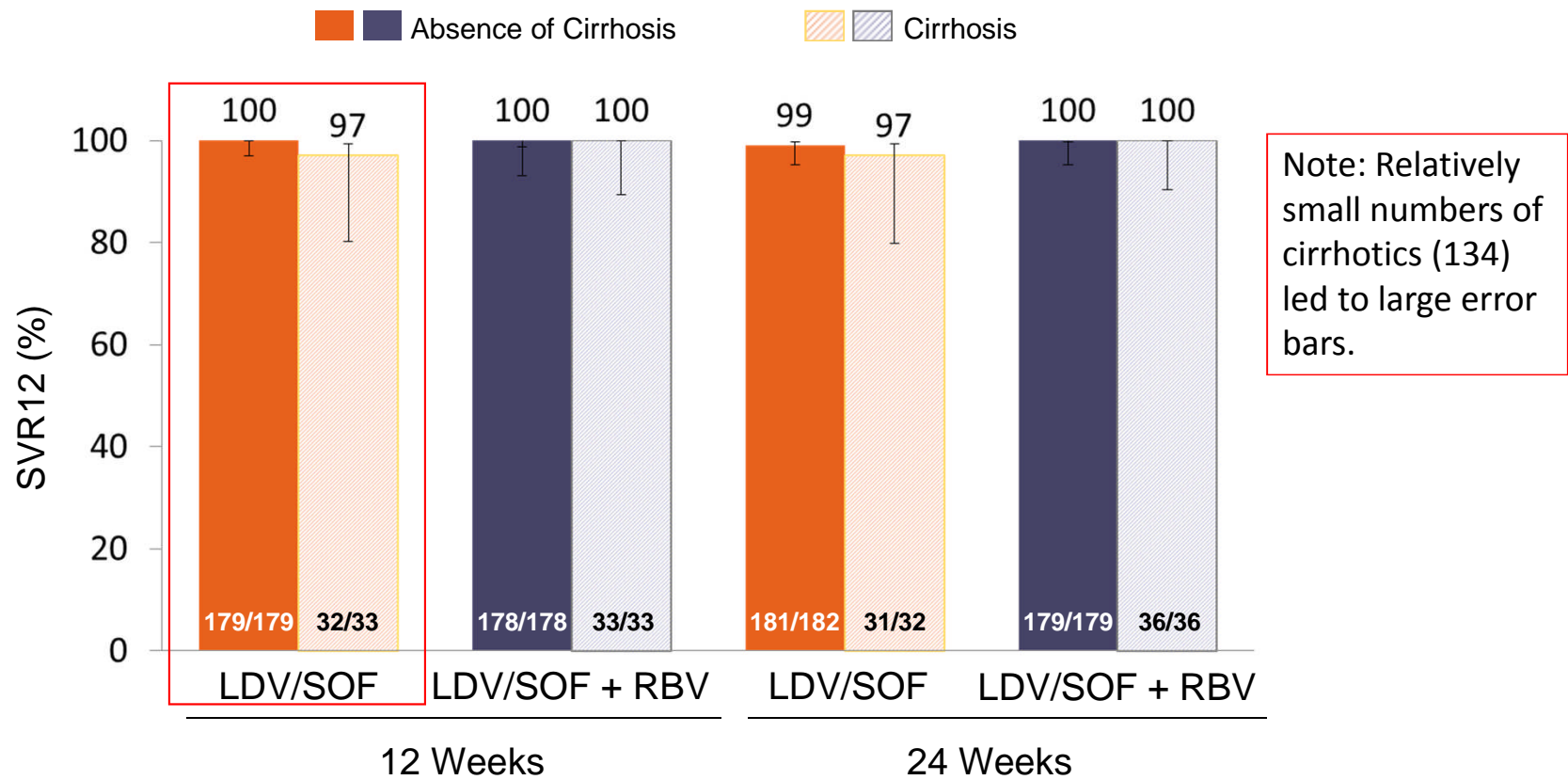
Error bars represent 95% confidence intervals.

Afdhal N, et al. *N Engl J Med* 2014; 2014 Apr 12 [Epub ahead of print]

ION-1 (LDV/SOF±RBV x 12 or 24 weeks)

†

TN: SVR12 Not Impacted by Treatment Duration (12 vs. 24 wks), Ribavirin, or Cirrhosis

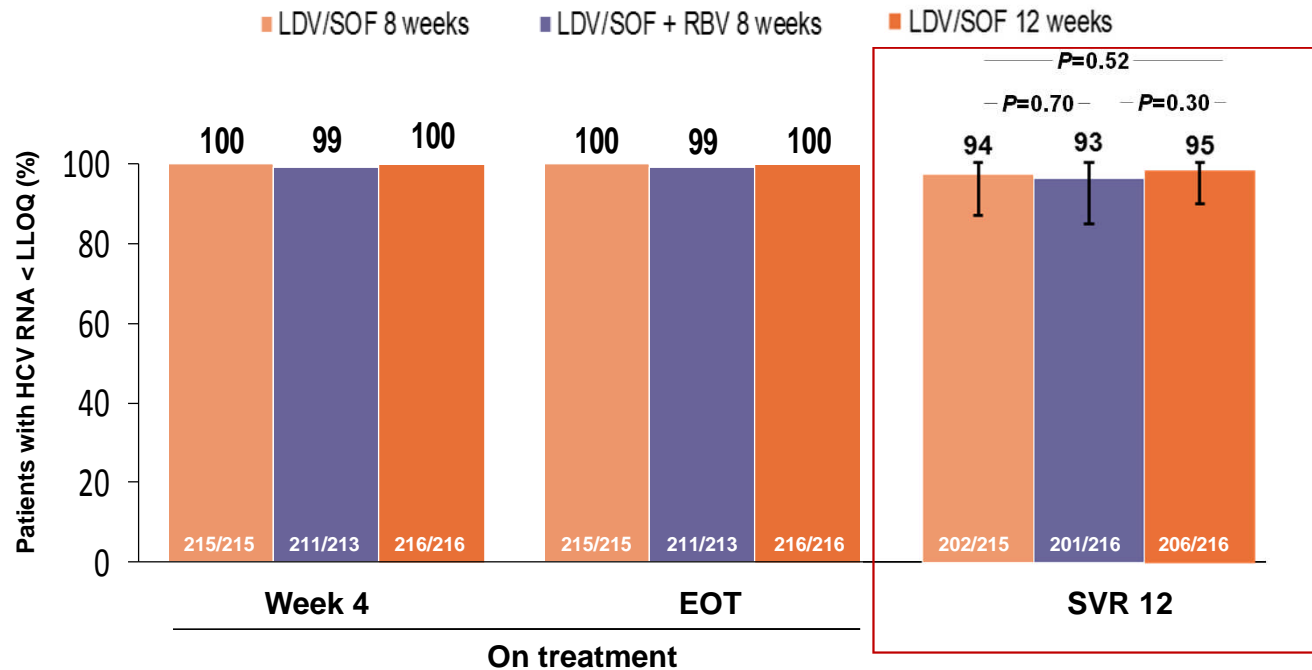


Error bars represent 95% confidence intervals  
Mangia A, EASL, 2014, O164  
Afdhal N, et al. *N Engl J Med* 2014; 2014 Apr 12 [Epub ahead of print]

ION-3 (LDV/SOF±RBV x 8 or 12 weeks)

†

## TN Non-cirrhotic: SVR12 Not Impacted by Treatment Duration (8 vs. 12 wks), Ribavirin



- All three treatment arms met the primary endpoint of superiority over the historical response rate of 60% ( $P<0.001$  for all comparisons)
- 8 weeks of LDV/SOF was non-inferior to 8 weeks of LDV/SOF + RBV and 12 weeks LDV/SOF
- 18% had NS5A RAVs at baseline, with 90% achieving SVR

Error bars represent 95% confidence intervals

Kowdley K, et al. *N Engl J Med* 2014; 2014 Apr 11 [Epub ahead of print]

ION-3 (LDV/SOF±RBV x 8 or 12 weeks)



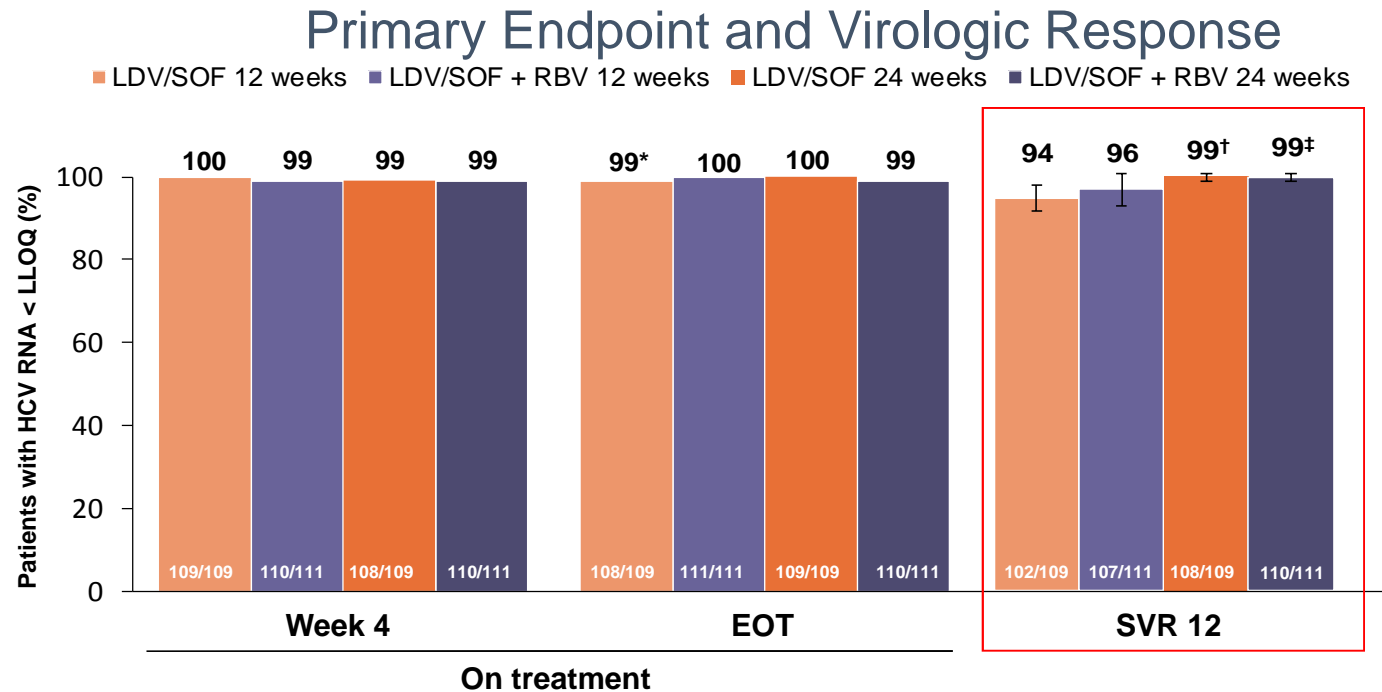
# Adverse Events (≥ 5% in Any Arm)

Preferred term, n (%)	LDV/SOF 8 wk n=215	LDV/SOF + RBV 8 wk n=216	LDV/SOF 12 wk n=216
Overall	145 (67)	165 (76)	149 (69)
Fatigue	45 (21)	75 (35)	49 (23)
Headache	30 (14)	54 (25)	33 (15)
Nausea	15 (7)	38 (18)	24 (11)
Insomnia	11 (5)	26 (12)	15 (7)
Irritability	3 (1)	29 (13)	9 (4)
Diarrhea	15 (7)	13 (6)	9 (4)
Arthralgia	9 (4)	11 (5)	16 (7)
Constipation	9 (4)	13 (6)	8 (4)
Dizziness	6 (3)	13 (6)	9 (4)
Rash	3 (1)	19 (9)	5 (2)
Pruritus	2 (<1)	16 (7)	5 (2)
Cough	3 (1)	12 (6)	7 (3)
Anemia	2 (<1)	17 (8)	2 (<1)
Muscle Spasms	3 (1)	11 (5)	6 (3)
Dyspnea	0	11 (5)	1 (<1)

ION-2 (LDV/SOF±RBV x 12 or 24 weeks)

‡

LDV/SOF Single Tablet Regimen ± RBV in Treatment-Experienced GT 1 HCV



\* One patient had an HCV RNA level of 42 IU/mL at the Week 12 visit, but had undetectable HCV RNA at post-treatment Weeks 4, 12, and 24

† One patient withdrew consent after the post-treatment Week 4 visit, at which time HCV RNA < 25 IU/mL

‡ This patient was non-adherent to study treatment as documented by plasma concentrations below or near the lower level of quantitation of LDV and GS-331007 (the predominant circulating metabolite of SOF) and at Weeks 2, 4, and 6

- All four treatment arms met the primary endpoint of superiority over the historical response rate of 25% ( $P < 0.001$  for all comparisons)
- 14% had NS5A RAVs at baseline, with 89% achieving SVR

Error bars represent 95% confidence intervals

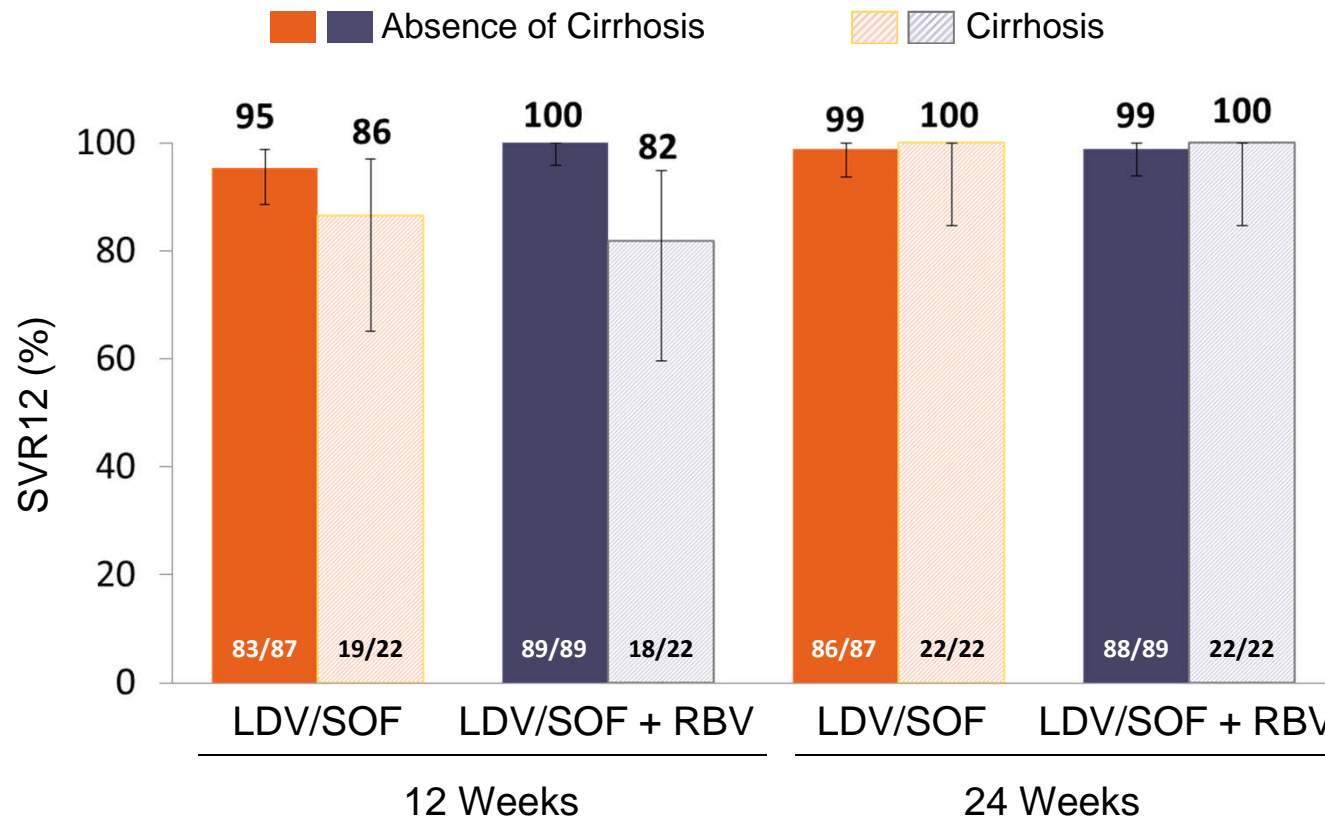
Afdhal N, EASL, 2014, O109

Afdhal N, et al. *N Engl J Med* 2014; 2014 Apr 12 [Epub ahead of print]

ION-2 (LDV/SOF±RBV x 12 or 24 weeks)

‡

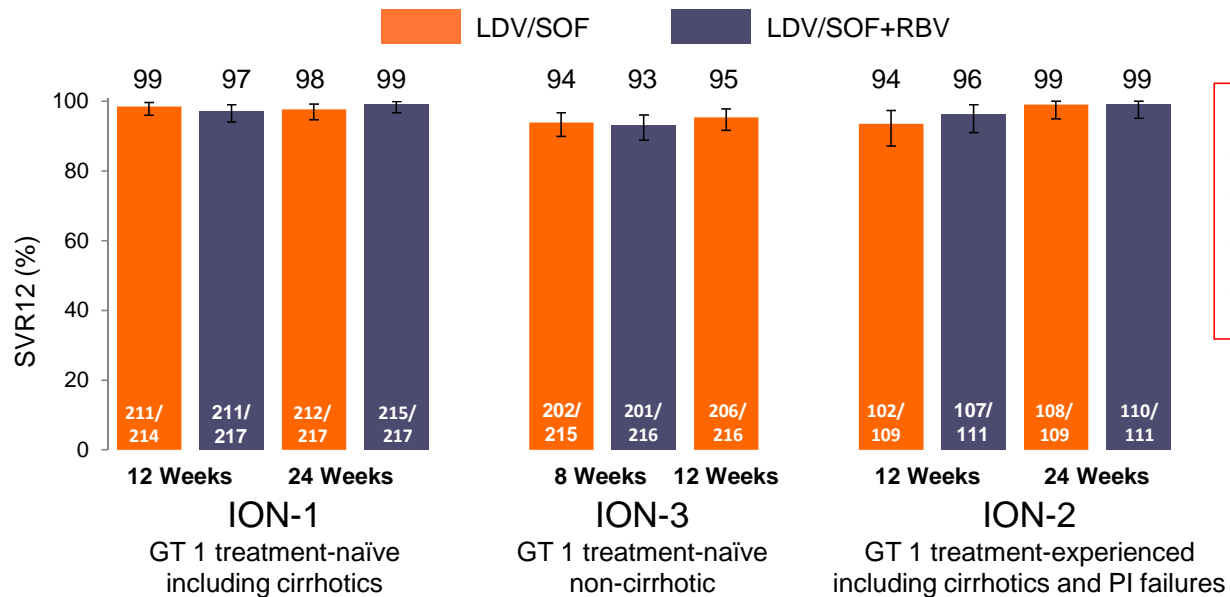
Increased SVR with 24 weeks in TE Cirrhotics (riba no apparent impact)



Note: Relatively small numbers of cirrhotics (88) led to large error bars particularly with 12 weeks of therapy. However, 44/44 TE cirrhotics achieved SVR with 24 weeks of therapy!

Error bars represent 95% confidence intervals  
Afdhal N, EASL, 2014, O109  
Afdhal N, et al. *N Engl J Med* 2014; 2014 Apr 12 [Epub ahead of print]

## Efficacy Summary



Riba: No Impact  
 TN Non-cirrhotic: 8 wks  
 TN Cirrhotic: 12 wks  
 TE Non-cirrhotic: 12 wks  
 TE Cirrhotic: 24 wks

222 cirrhotics split in 8 arms leads to some uncertainty with relatively large error bars.

- 97% (1886/1952) overall SVR rate
- 3% (66/1952) did not achieve SVR
  - 1.4% (28) LTFU
  - 0.1% (2) virologic breakthrough (both due to non-adherence)
  - 1.8% (36) relapsed. Patients may be rolled over to a retreatment study

Error bars represent 95% confidence intervals.

Afdhal N, et al. *N Engl J Med* 2014; 2014 Apr 12 [Epub ahead of print]

Kowdley K, et al. *N Engl J Med* 2014; 2014 Apr 11 [Epub ahead of print]

Afdhal N, et al. *N Engl J Med* 2014; 2014 Apr 12 [Epub ahead of print]

# AbbVie HCV Clinical Development Program

## ABT-450/RTV/ABT-267+ABT-333±RBV in GT 1 Patients



Trial	Pt type	Treatment duration	SVR12
<b>SAPPHIRE-I</b>	GT1, TN n=631	12 wks + riba	<ul style="list-style-type: none"> <li>•96% overall</li> <li>•GT1a – 95%</li> <li>•GT1b – 98%</li> </ul>
<b>PEARL-IV</b>	GT1a, TN n=305	12 wks +/- riba	<ul style="list-style-type: none"> <li>•92% overall</li> <li>•90% no RBV</li> <li>•97% + RBV</li> </ul>
<b>PEARL-III</b>	GT1b, TN n=410	12 wks +/- riba	<ul style="list-style-type: none"> <li>•99% overall</li> <li>•99% +/- RBV</li> </ul>
<b>SAPPHIRE-II</b>	GT1, TE n=394	12 wks + riba	<ul style="list-style-type: none"> <li>•96% overall</li> <li>•GT1a – 96%</li> <li>•GT1b – 97%</li> </ul>
<b>PEARL-II</b>	GT1b, TE n= 179	12 wks +/- riba	<ul style="list-style-type: none"> <li>•98% overall</li> <li>•100% no RBV</li> <li>•97% + RBV</li> </ul>
<b>TURQUOISE-II</b>	GT1, compensated cirrhosis, TN, TE n=380	12 or 24 wks + riba	<ul style="list-style-type: none"> <li>•94% overall</li> <li>•92% 12 wks</li> <li>•96% 24 wks</li> </ul>

### Generic Drug Names

ABT-333 = Dasabuvir (NNI)

ABT-267 = Ombitasvir (NS5A)

ABT-450 = Veruprevir (PI)

### Target Profile

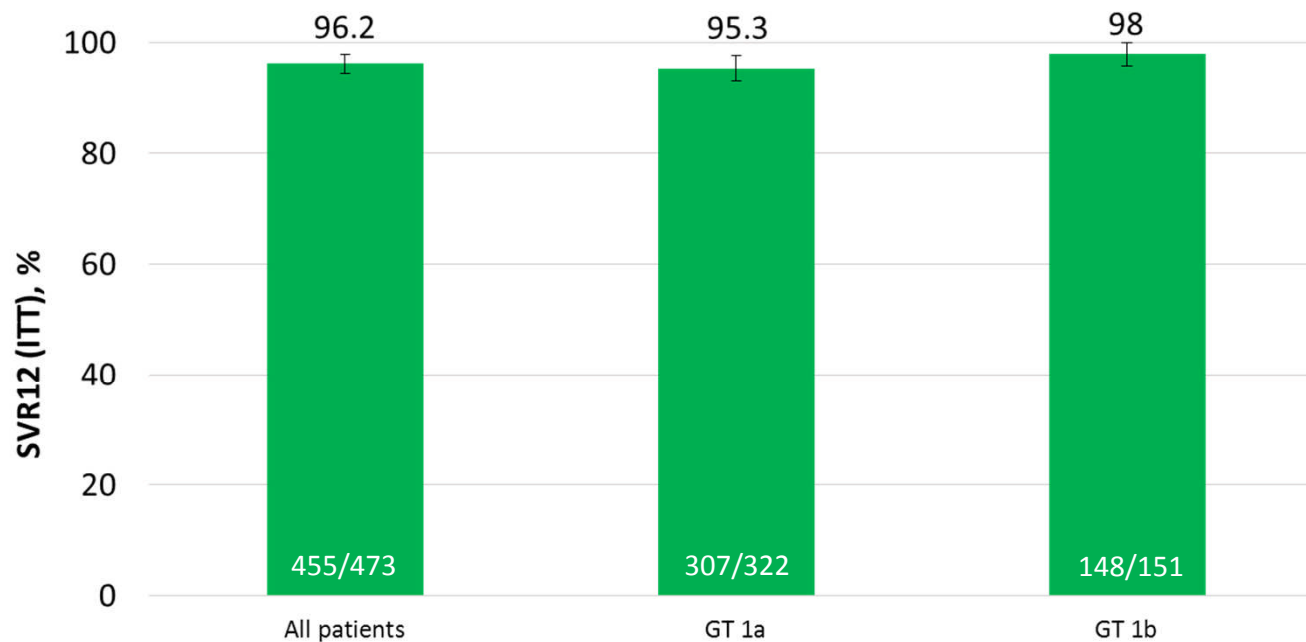
- FDC ABT-450/RTV/ABT-267 dosed QD (2 pills)
- ABT-333 dosed BID (1 pill)
- RBV dosed BID
- 12 week treatment duration for non-cirrhotic patients

SAPPHIRE-I: Feld et al. NEJM. April 11, 2014; SAPPHIRE-II: Zeuzem et al. NEJM. April 10, 2014  
PEARL-III: P. Ferenci, EASL 2014, P1299LB; TURQUOISE-II: Poordad et al. NEJM. April 12, 2014  
PEARL-II & PEARL-IV: AbbVie press release, January 31, 2014 and DDW May 3-6, 2014

SAPPHIRE I (ABT-450+RTV+ombitasvir+dasabuvir+RBV): GT1

†

## ABT-450+RTV+Ombitasvir+Dasabuvir+RBV for 12 Weeks in GT 1 Treatment-Naïve, Non-Cirrhotic Patients



- On treatment virologic breakthrough: 1 (0.2%)
- Relapse post-treatment: 7/463 (1.5%)

Patients missing data in SVR12 window count as failures

Feld JJ, EASL, 2014, O60

Feld JJ, et al. *N Engl J Med* 2014; 2014 Apr 11 [Epub ahead of print]

# Adverse Events

	ABT-450+RTV+ombitasvir +dasabuvir+RBV N=473	Placebo N=158	P-value
Any AE, n (%)	414 (87.5)	116 (73.4)	<0.05
Fatigue, n (%)	164 (34.7)	45 (28.5)	NS
Headache, n (%)	156 (33.0)	42 (26.6)	NS
Nausea, n (%)	112 (23.7)	21 (13.3)	<0.05
Pruritus, n (%)	80 (16.9)	6 (3.8)	<0.05
Insomnia, n (%)	66 (14.0)	12 (7.6)	<0.05
Diarrhea, n (%)	65 (13.7)	11 (7.0)	<0.05
Asthenia, n (%)	57 (12.1)	6 (3.8)	<0.05
Rash, n (%)	51 (10.8)	9 (5.7)	NS
Dizziness (%)	8.0%	3.8%	NS
Dyspnea (%)	8.0%	2.5%	<0.05
Dry skin (%)	5.7%	0.6%	<0.05
Anemia (%)	5.3%	0	<0.05

- The AEs were more common with ABT-450+RTV+ombitasvir+dasabuvir+RBV than placebo.
- AEs that occurred more frequently with active therapy than placebo included nausea, pruritus, insomnia, diarrhea, and asthenia

## Laboratory Abnormalities

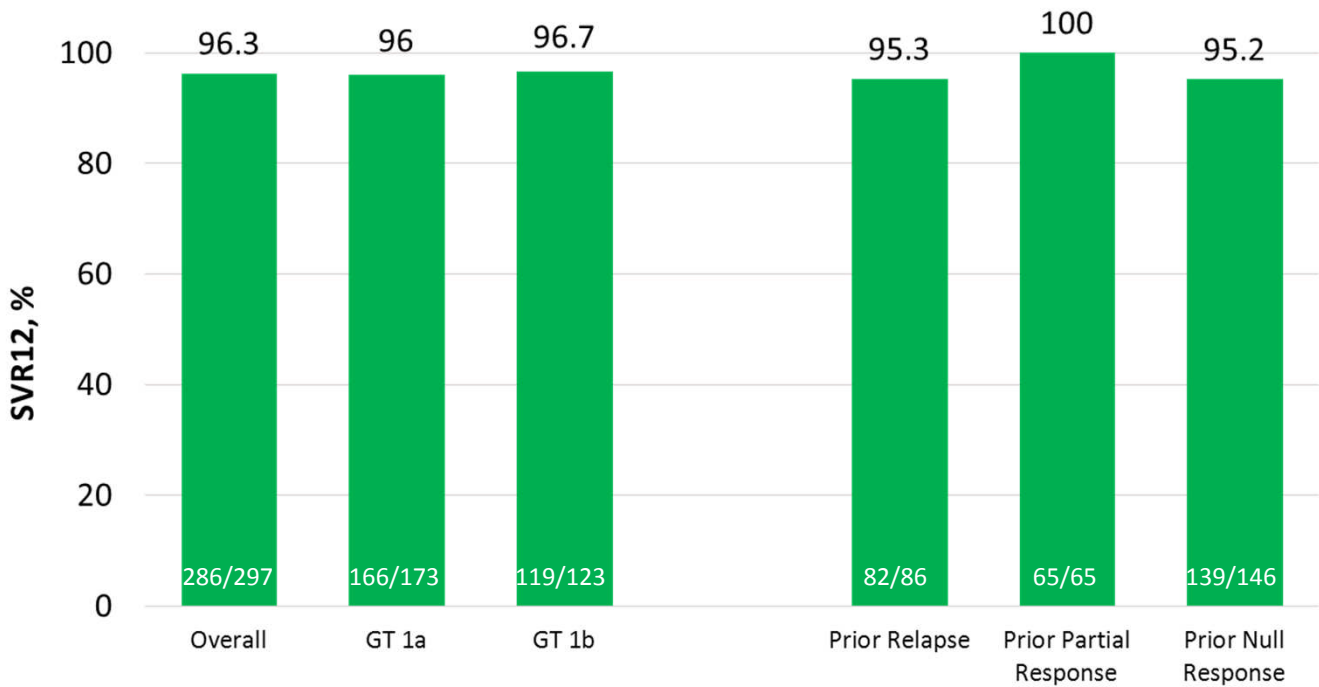
- Baseline Hgb >13 g/dL (male) or >12 g/dL (female)
- Absolute neutrophil count and platelet data not reported
- No discontinuations due to lab abnormalities
- Elevations in total bilirubin were mainly transient and predominantly indirect bilirubin; no cases consistent with Hy's Law
- 1 patient received EPO; no patient was transfused
- RBV dose was modified due to AEs in 26 (5.5%) of those on the 5 drug regimen

	450+RTV+ombitasvir+dasabuvir+RBV N=473	450+RTV+ombitasvir+dasabuvir+RBV as placebo N=158
Grade 3-4 laboratory abnormality, n (%)	20 (4.2)	10 (6.3)
ALT >5X ULN	4/469 (0.9)	7/158 (4.4)
AST >5X ULN	3/469 (0.6)	3/158 (1.9)
Alkaline phosphatase >5X ULN	0	0
Total bilirubin >3X ULN	13/469 (2.8)	0
Hemoglobin		
Grade 1 (<LLN-10.0 g/dL)	223/469 (47.5)	4/158 (2.5)
Grade 2 (<10.0-8.0 g/dL)	27/469 (5.8)	0/158
Grade 3 (<8.0-6.5 g/dL)	0/469	0/158
Grade 4 (<6.5 g/dL)	0/469	0/158





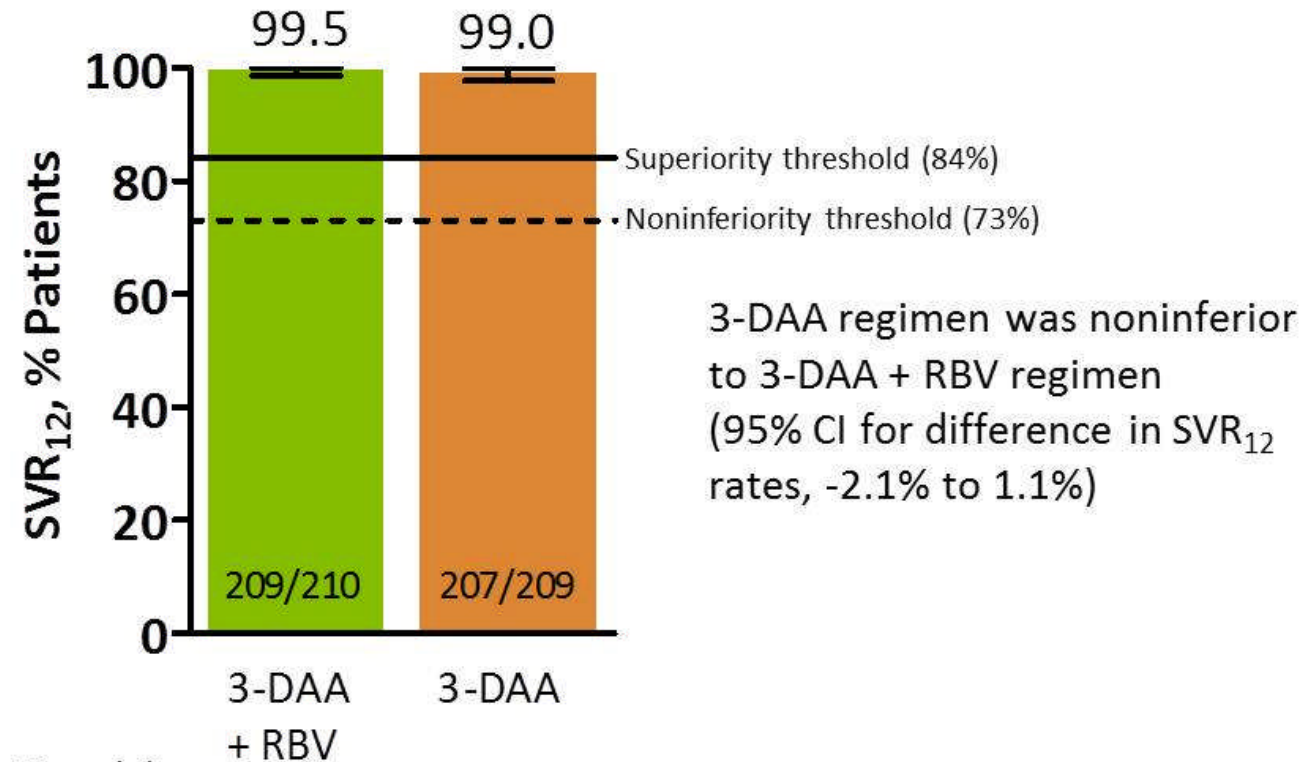
ABT-450+RTV+Ombitasvir+Dasabuvir+RBV for 12 Weeks in GT 1  
Treatment-Experienced, Non-Cirrhotic Patients



Patients missing data in SVR12 window count as failures  
Zeuzem S, EASL, 2014, O1  
Zeuzem S, et al. *N Engl J Med* 2014; 2014 Apr 11 [Epub ahead of print]

PEARL III – Naïve  
non-cirrhotic Ib.

$SVR_{12} \geq 99\%$  Achieved After 12 Weeks with 3-DAA  $\pm$  RBV



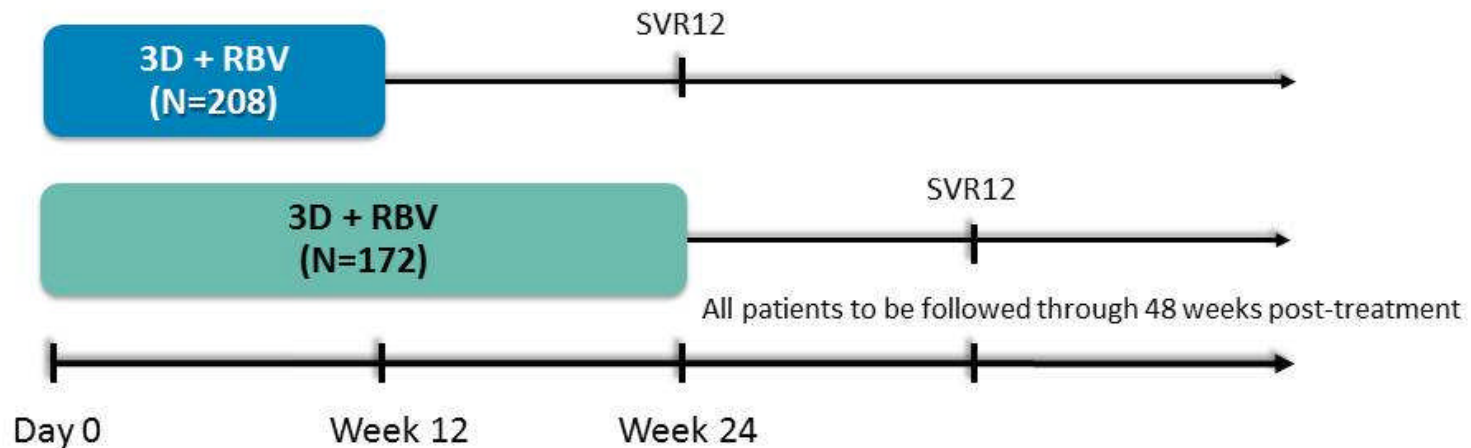
ITT population

Dashed horizontal line depicts noninferiority threshold

Solid horizontal line depicts superiority threshold

Adapted from the K Rajender Reddy presentation at CROI on March 4, 2014

## TURQUOISE-II Study Design: Phase 3 Trial Conducted Exclusively in GT1-Infected Cirrhotic Patients (N=380)

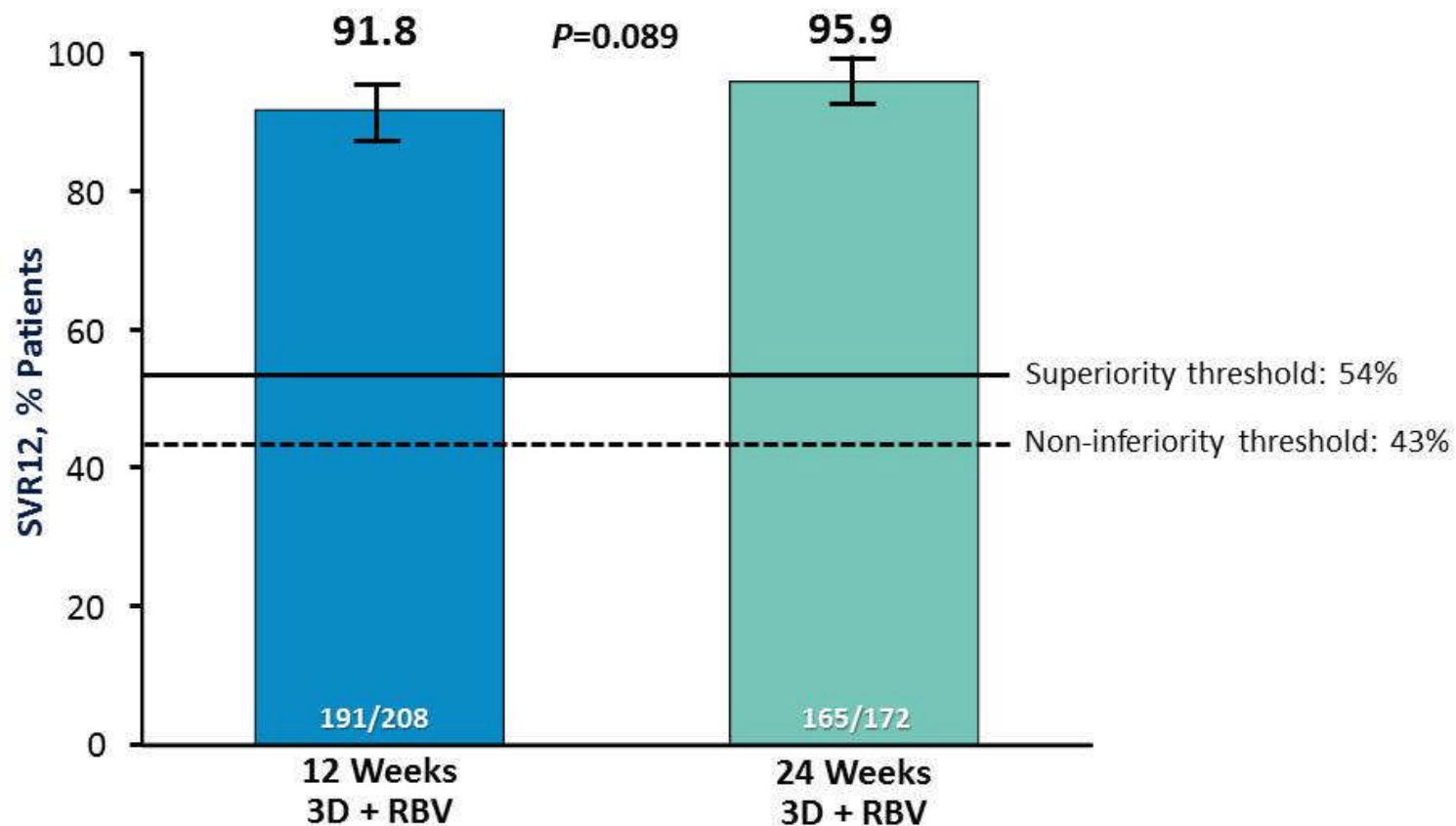


3D: co-formulated ABT-450/r/ombitasvir, 150 mg/100 mg/25 mg QD; dasabuvir, 250 mg BID

RBV: 1000-1200 mg daily according to body weight (<75 kg and  $\geq$ 75kg, respectively)

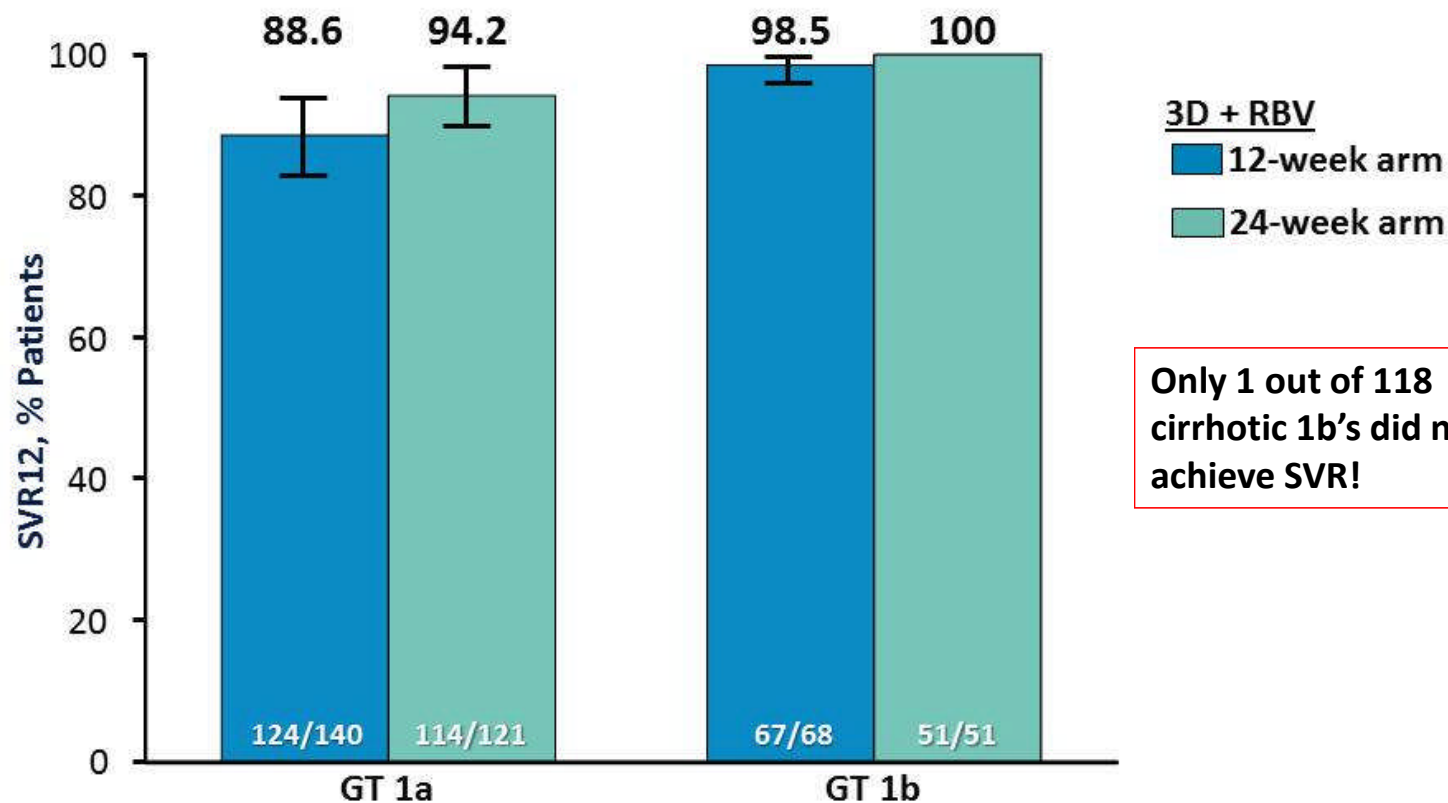
Adapted from the Fred Poordad presentation at ILC/EASL on April 12, 2014

## TURQUOISE-II Results: ITT SVR12 Rates of 92% to 96%



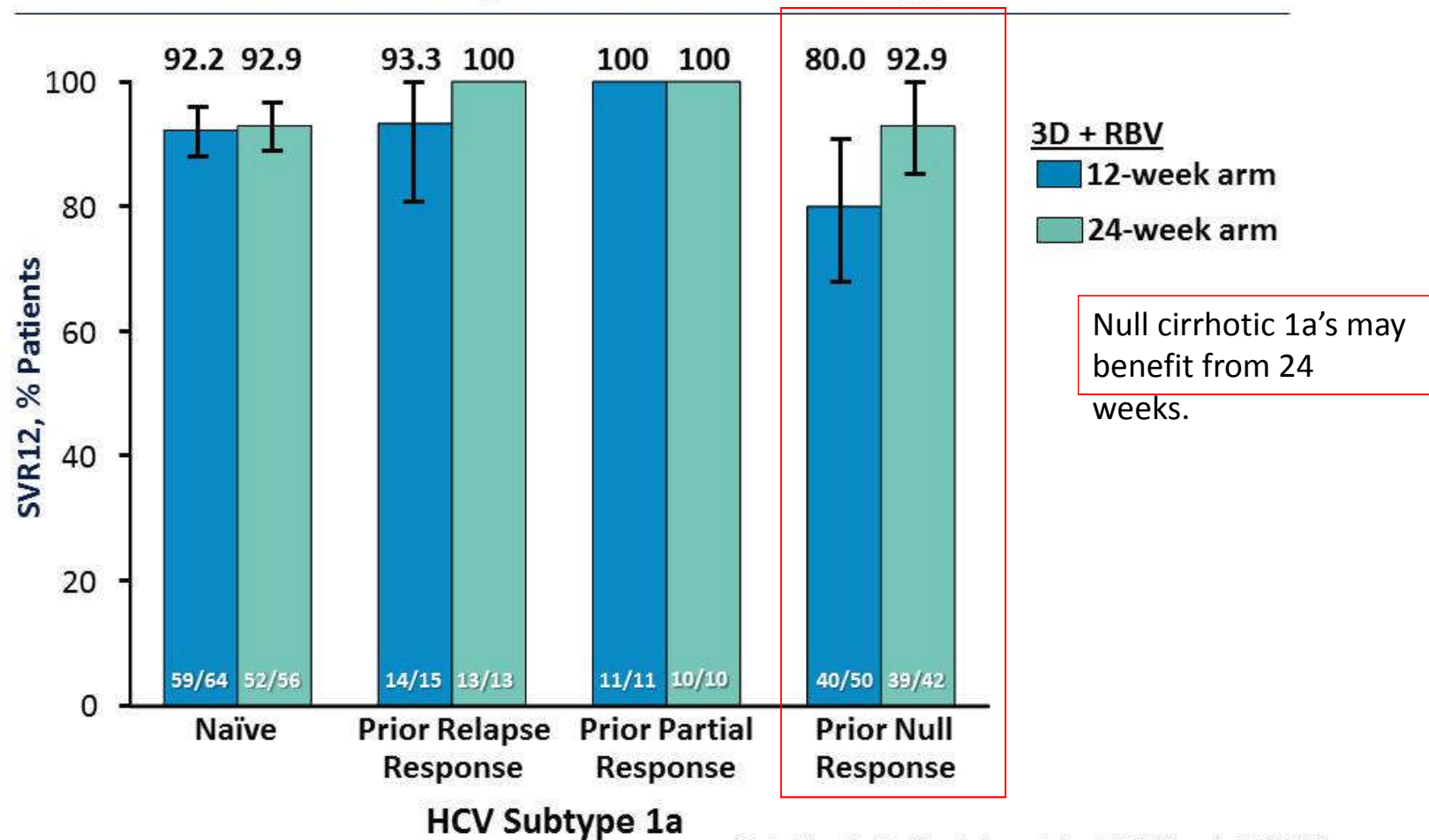
Adapted from the Fred Poordad presentation at ILC/EASL on April 12, 2014

## TURQUOISE-II Results: ITT SVR12 Rates by HCV Subtype



Only 1 out of 118  
cirrhotic 1b's did not  
achieve SVR!

## TURQUOISE-II Results: ITT SVR12 Rates by Prior Treatment Response in HCV Subtype 1a



Adapted from the Fred Poordad presentation at ILC/EASL on April 12, 2014

# AbbVie HCV Clinical Development Program

## ABT-450/RTV/ABT-267+ABT-333±RBV in GT 1 Patients

‡

Trial	Pt type	Treatment duration	SVR12
<b>SAPPHIRE-I</b>	GT1, TN n=631	12 wks + riba	<ul style="list-style-type: none"> <li>•96% overall</li> <li>•GT1a – 95%</li> <li>•GT1b – 98%</li> </ul>
<b>PEARL-IV</b>	GT1a, TN n=305	12 wks +/- riba	<ul style="list-style-type: none"> <li>•92% overall</li> <li>•90% no RBV</li> <li>•97% + RBV</li> </ul>
<b>PEARL-III</b>	GT1b, TN n=410	12 wks +/- riba	<ul style="list-style-type: none"> <li>•99% overall</li> <li>•99% +/- RBV</li> </ul>
<b>SAPPHIRE-II</b>	GT1, TE n=394	12 wks + riba	<ul style="list-style-type: none"> <li>•96% overall</li> <li>•GT1a – 96%</li> <li>•GT1b – 97%</li> </ul>
<b>PEARL-II</b>	GT1b, TE n= 179	12 wks +/- riba	<ul style="list-style-type: none"> <li>•98% overall</li> <li>•100% no RBV</li> <li>•97% + RBV</li> </ul>
<b>TURQUOISE-II</b>	GT1, compensated cirrhosis, TN, TE n=380	12 or 24 wks + riba	<ul style="list-style-type: none"> <li>•94% overall</li> <li>•92% 12 wks</li> <li>•96% 24 wks</li> </ul>

1a TN/TE: 3D+R x 12 wks

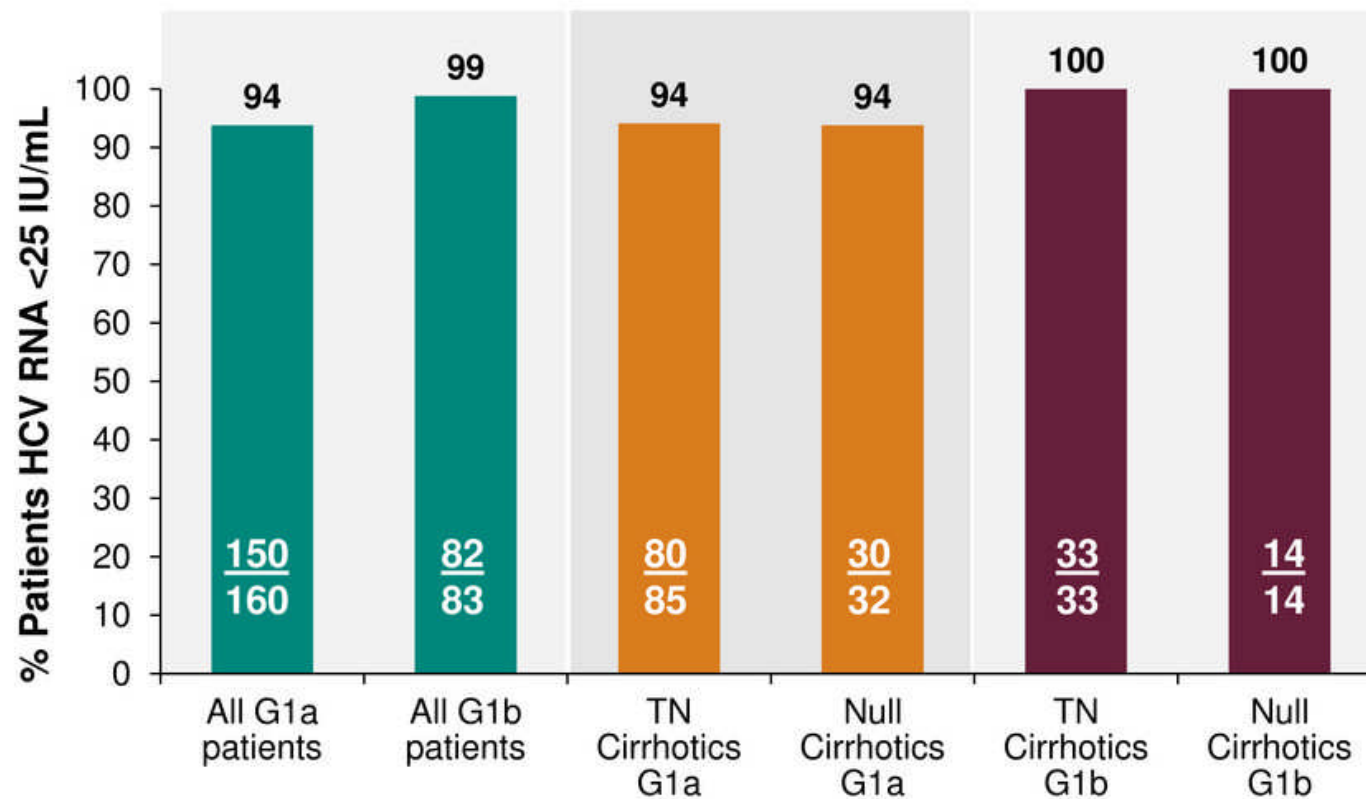
1b TN/TE: 3D x 12 wks

\*1a cirrhotic nulls require 24 weeks

\*1b cirrhotics require ribavirin?

SAPPHIRE-I: Feld et al. NEJM. April 11, 2014; SAPPHIRE-II: Zeuzem et al. NEJM. April 10, 2014  
PEARL-III: P. Ferenci, EASL 2014, P1299LB; TURQUOISE-II: Poordad et al. NEJM. April 12, 2014  
PEARL-II & PEARL-IV: AbbVie press release, January 31, 2014 and DDW May 3-6, 2014

## HCV: MK-5172/MK-8742 Treatment Yields Similar Responses Irrespective of Prior Response to Other Therapies



# Conclusions

- New IFN-Free Regimens for G1: 8-24 weeks, with or without ribavirin.
- Simeprevir+sofosbuvir+/-riba x 12 wks: Currently off-label. Concerns exist over small numbers, 12 week duration for TE cirrhotics.
- BMS: daclatasvir+asunaprevir x 24 wks (1b).
- Gilead: sofosbuvir+ledipasvir x 12 wks (8 wks for TN non-cirrhotic and 24 weeks for TE cirrhotics).
- AbbVie: ABT-450/RTV+ombitasvir+dasabuvir+/-RBV: 1a, 3D+R x 12 weeks (24 weeks for cirrhotic nulls); 1b, 3D x 12 weeks (3D+R x 12 weeks in cirrhotics).
- Merck: 5172/8742 FDC appears promising but won't be available in the near future.

